Docket No.: 649218008US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Michael D. Laufer

Application No.: 10/810,276 Confirmation No.: 8525

Filed: March 26, 2004 Art Unit: 3769

For: METHOD OF TREATING AIRWAYS IN THE LUNG Examiner: D. M. Shay

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

As required under § 41.37(a), this brief is filed more than two months after the 21 May 2009 filing date of the Notice of Appeal in this case, and it is in furtherance of the Notice of Appeal.

The fees required under § 41.20(b)(2) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and MPEP § 1205.2:

I. Real Party In Interest
II Related Appeals and Interferences
III. Status of Claims
IV. Status of Amendments
V. Summary of Claimed Subject Matter

I. REAL PARTY IN INTEREST

The real party in interest is Asthmatx, Inc., the assignee of record of all right, title and interest in the present application.

II. RELATED APPEALS AND INTERFERENCES

An appeal is pending in U.S. Application No. 09/095,323, to which the present application claims priority. Neither Appellant, Appellant's legal representative, nor the above-identified Assignee are aware of any other appeals or interferences that are related to, will directly affect or be directly affected by, or have a bearing on the Board's decision in the present appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 7 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 4-6, 8 and 11-14
2. Claims withdrawn from consideration but not canceled: None
3. Claims pending: 1-3, 7, 9, 10 and 15
4. Claims allowed: None
5. Claims rejected: 1-3, 5-11 and 13-15

C. Claims On Appeal

The claims on appeal are claims 1-3, 7, 9, 10 and 15

IV. STATUS OF AMENDMENTS

Appellant filed an Amendment on 22 July 2008. These amendments were considered and no new matter objections or rejections were raised in a Non-Final Action dated 21 January 2009. The Appellant also filed an Amendment on 21 May 2009 along with the Notice of Appeal in which claim 9 was amended to put this claim in better condition for appeal, and claims 5, 6, 8, 11, 13 and 14 were canceled. The Examiner has not issued an Advisory Action in response to the Amendment filed on 21 May 2009. The Appellant respectfully requests that the amendments set forth in the Amendment dated 21 May 2009 be entered for consideration.

V. SUMMARY OF CLAIMED SUBJECT MATTER

A. Overview of Appellant's Technology

The subject matter defined by the claims involved in the present appeal is directed to a method for treating asthma and a method for controlling mucus within a lung.

B. Claims on Appeal

Each claim being appealed is paraphrased below, with citations to the corresponding portions of the specification and drawings as required by 37 C.F.R. § 41.37(c)(1)(v). These citations are provided in order to illustrate specific examples and embodiments of the recited claim language, and are not intended to limit the claims.

1. Claim 1

Claim 1 is directed to a method of treating asthma comprising selecting an airway for treatment, wherein the airway has hypertrophied airway smooth muscle. (Specification at, for example, p. 4, ll. 1-3; p. 5, ll. 25-27; p. 6, ln. 12 to p. 11, ln. 9.) Claim 1 further includes irradiating a length of the airway with a light source having a wavelength of about 240 nm to about 280 nm and an intensity which causes a change in the airway such that a thickness of the airway smooth muscle decreases and

bronchoconstriction of the airway is reduced. (Specification at, for example, p. 6, ll. 6-20; p. 7, ll. 15-20; p. 10, ll. 25-28; p. 11, ll. 5-9.)

2. Claim 2

Claim 2 is directed to a method of treating asthma as set forth in claim 1, where the change in the airway occurs in smooth muscle cells. (Specification at, for example, p. 6, ll. 6-20.)

3. Claim 3

Claim 3 is directed to a method of treating asthma as set forth in claim 1, where the change in the airway occurs in mucus gland cells. (Specification at, for example, p. 6, ll. 20-23.)

4. Claim 7

Claim 7 is directed to a method of treating asthma as set forth in claim 1, further comprising moving the light source along the airway. (Specification at, for example, p. 7, ll. 5-11.)

5. Claim 9

Claim 9 is directed to a method of treating asthma as set forth in claim 1, where the change in the airway comprises preventing airway cells from replicating. (Specification at, for example, p. 6, ll. 12-15.)

6. Claim 10

Claim 10 is directed to a method of controlling mucus within a lung comprising selecting an airway for treatment. (Specification at, for example, p. 6, ll. 6-20.) Claim 10 further includes irradiating a length of the airway with a light source having a wavelength of about 240 nm to about 280 nm and an intensity which causes a change in airway mucus gland cells such that mucus secretions of the airway are reduced. (Specification at, for example, p. 6, ll. 6-20; p. 7, ll. 15-20; p. 10, ll. 25-28.)

7. Claim 15

Claim 15 is directed to a method of controlling mucus within a lung as set forth in claim 10, further comprising moving the light source along the airway. (Specification at, for example, p. 7, ll. 5-11.)

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. The Examiner's Rejections

1. The Examiner rejected claims 1-3, 5-11 and 13-15 under 35 U.S.C. § 112, first paragraph.

2. The Examiner rejected claims 1-3, 5-11 and 13-15 under 35 U.S.C. § 112, second paragraph.

3. The Examiner rejected claims 1-3, 5-11 and 13-15 under 35 U.S.C. § 102(b) over Ivanyuta et al., *Effect of Low-Power Laser Irradiation of Bronchial Mucosa on the State of Systemic and Local Immunity in Patients with Chronic Bronchitis* ("Ivanyuta").

4. The Examiner rejected claims 1-3, 5-11 and 13-15 under 35 U.S.C. § 103(a) over the combination of James et al., *The Mechanics of Airway Narrowing in Asthma* ("James"), U.S. Patent No. 5,053,033 ("Clarke"), International Publication No. WO97/37715 ("Waksman"), and U.S. Patent No. 5,574,059 ("Regunathan");

5. The Examiner rejected several different combinations of the pending claims under the doctrine of obviousness-type double patenting as being unpatentable over one or more claims of (a) U.S. Patent Nos. 7,027,869, 6,634,363, 6,411,852, 6,299,633, 6,283,989, 6,283,988, 6,200,333, 6,083,255, 6,273,907, 6,488,673, 7,264,002, 7,273,055 and 5,972,026, and (b) U.S. Patent Application Nos. 11/608,606, 11/562,925, 11/398,353, 11/408,668, 11/420,442, 11/361,564, 11/117,905,

11/617,512, 11/614,914, 11/534,621, 11/614,919, 11/612,620, 11/618,533, 11/609,242, 11/425,345, 11/421,444, 09/095,323 and 11/562,910.

B. The Issues on Appeal

1. Whether the Examiner erred in rejecting pending claims 1-3, 7, 9, 10 and 15 under 35 U.S.C. § 112, first paragraph.

2. Whether the Examiner erred in rejecting pending claims 1-3, 7, 9, 10 and 15 under 35 U.S.C. § 112, second paragraph.

3. Whether the Examiner erred in rejecting pending claims 1-3, 7, 9, 10 and 15 under 35 U.S.C. § 102(b) over Ivanyuta.

4. Whether the Examiner erred in rejecting pending claims 1-3, 7, 9, 10 and 15 over the combination of James, Clarke, Waksman and Regunathan under 35 U.S.C. § 103.

5. Whether the Examiner erred in rejecting pending claims 1-3, 7, 9, 10 and 15 under the doctrine of obviousness-typed double patenting over (a) U.S. Patent Nos. 7,027,869, 6,634,363, 6,411,852, 6,299,633, 6,283,989, 6,283,988, 6,200,333, 6,083,255, 6,273,907, 6,488,673, 7,264,002, 7,273,055 and 5,972,026, and (b) U.S. Patent Application Nos. 11/608,606, 11/562,925, 11/398,353, 11/420,442, 11/361,564, 11/117,905, 11/617,512, 11/614,914, 11/534,621, 11/614,919, 11/612,620, 11/618,533, 11/609,242, 11/425,345, 11/421,444, and 11/562,910.

VII. ARGUMENT

A. Section 112, First Paragraph, Rejection of Claims 1-3, 5-11 and 13-15

Claims 1-3, 5-11 and 13-15 were rejected under 35 U.S.C. § 112, first paragraph. Claims 5, 6, 8, 11, 13 and 14 were canceled in the Amendment filed on 21 May 2009. Claims 1-3, 7, 9, 10 and 15 are the remaining pending claims subject to this rejection,

and therefore the following remarks address only the rejection of claims 1-3, 7, 9, 10 and 15.

1. Legal Standard for Enablement

35 U.S.C. § 112, first paragraph, requires "the specification shall contain a written description of the invention, and the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, ... to make and use the same." To satisfy the enablement requirement, the disclosure in an application must contain sufficient information regarding the subject matter of the claims to enable a person skilled in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ 2d at 1404 (Fed. Cir. 1988); MPEP § 2164.01. The fact that experimentation may be complex does not necessarily make it undo experimentation if the art typically engages in such experimentation. *Id.* The test of enablement is not whether any experimentation is necessary, but rather if the necessary experimentation is undo. MPEP § 2164.01. For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undo experimentation. MPEP § 2164.01(c).

2. The Examiner's Basis for Rejection

Claims 1-3, 5-11 and 13-15 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the disclosure does not teach how radiation with a wavelength of about 240 nm to about 280 nm could be effectively applied to mucus cells that lie below the smooth muscle cells. The Examiner cites James for the proposition that the airway smooth muscle, submucosa and epithelium layers are about 65 microns thick in even the smallest bronchioles, and the Examiner cites U.S. Patent No. 4,784,135 ("Blum") for the proposition that "ultraviolet wavelengths are strongly absorbed and extinguished within a few microns (see Blum et al. column 4, lines 55-68)." The Examiner states

"Further the treatment would be ineffective due to shadowing, as set forth in paragraph 20 of the Laufer Declaration."

3. Appellant's Position

The rejection of claims 1, 2, 7 and 9 under 35 U.S.C. § 112, first paragraph, is incorrect because these claims do not include effecting the mucus cells. Only claims 3, 10 and 15 include changing airway mucus glands. Therefore, the rejection of claims 1, 2, 7 and 9 under 35 U.S.C. § 112, first paragraph, is incorrect on its face because these claims do not include the subject matter that the Examiner asserts is not enabled by the originally filed disclosure.

The rejection of claims 3, 10 and 15 under Section 112, first paragraph, is also incorrect because (a) the Examiner mischaracterizes both James and Blum. The Examiner asserts that James teaches the submucosa and epithelium cells are about "65 microns thick." The Examiner's understanding of James is simply wrong. The text of James cited by the Examiner does not state that the submucosa and epithelium layers are 65 μm thick, but rather James teaches that the wall "area" of 2 mm airways is 65 μm^2 (+/- 49 μm^2). The Examiner accordingly incorrectly characterizes the area (μm^2) of a cross-section of the airway as the airway wall thickness (μm). The single-dimensional wall thickness must be less than the two-dimensional wall area, and thus the wall thickness disclosed in James must be less than the 65 μm^2 wall area. Thus, the Examiner incorrectly equated the 65 μm^2 wall area directly with the wall thickness.

The Examiner's characterization of Blum is also incorrect because column 4, lines 55-68, of Blum teaches that radiation at 193 nm produces a groove approximately 150 μm deep. The Appellant does not see where Blum teaches "ultraviolet wavelengths are strongly absorbed and extinguished within a few microns" as the Examiner asserts. The Examiner, therefore, also incorrectly characterized Blum. For these reasons alone, the Examiner's analysis is incorrect and this rejection should be reversed.

The combination of James and Blum, moreover, actually supports the Appellant's position that claims 3, 10 and 15 are enabled by the original disclosure. More specifically, because the portion of Blum cited by the Examiner teaches that ultraviolet radiation at 193 nm produces a groove approximately 150 μm deep, the UV radiation taught by Blum can accordingly penetrate tissue to a depth of 150 μm – more than 200% deeper than the 65 micron nominal wall thickness that the Examiner purports is taught by James. The claimed UV radiation wavelength range of about 240 nm to about 280 nm is longer than 193 nm wavelength described by Blum, and thus the claimed wavelengths would be expected to penetrate to a depth greater than 150 μm at similar pulse-power parameters. As a result, the claimed wavelength range of about 240 nm to about 280 nm penetrates to a depth greater than either (a) the thickness of a wall having an area of approximately 65 μm^2 (+/- 49 μm^2) as disclosed in James or (b) the 65 μm nominal wall thickness that the Examiner asserts is present in small airways. A person of ordinary skill in the art, therefore, could implement the claimed methods using pulse-power parameters that reach the desired tissue without undo experimentation. The rejection of claims 3, 10 and 15 should accordingly be reversed for these reasons as well.

B. Section 112, Second Paragraph, Rejection of Claims 1-3, 5-11 and 13-15

Claims 1-3, 5-11 and 13-15 were rejected under 35 U.S.C. § 112, second paragraph. As noted above, claims 5, 6, 8, 11, 13 and 14 were canceled in the Amendment dated 21 May 2009. Therefore, this rejection pertains only to remaining claims 1-3, 7, 9, 10 and 15.

1. Legal Standard for Section 112, Second Paragraph

35 U.S.C. § 112, second paragraph, requires "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." The second requirement of this

section is objective because it does not depend on the views of the applicant or any particular individual, but rather is evaluated in the context of whether the claim is definite – i.e., whether the scope of the claim is "clear to a hypothetical person possessing the ordinary level of skill in the pertinent art." MPEP § 2171.

2. The Examiner's Basis for Rejection

In rejecting the pending claims under 35 U.S.C. § 112, second paragraph, the Examiner states that claims 1 and 10 are indefinite because the exact range to be encompassed by the term "a wavelength of about 240 nm to about 280 nm" is unclear on the grounds that this range seems to encompass (a) a wavelength of light "in the red visible range" as recited in dependent claims 5 and 13, and (b) radiation from "an infrared source, a visible source, or an ultraviolet source" as set forth in claims 6 and 14. This rejection accordingly stems from the range of wavelengths recited in independent claims 1 and 10 relative to the different wavelengths recited in corresponding dependent claims 5, 6, 13 and 14.

3. Appellant's Position

Claims 1 and 10 are definite under 35 U.S.C. § 112, second paragraph, in light of the cancellation of claims 5, 6, 13 and 14. The dependency of claims 5, 6, 13 and 14 from claims 1 or 10 was an inadvertent oversight caused by amending claims 1 and 10 to include the range of "about 240 nm to about 280 nm" in an Amendment dated 31 October 2007. Claims 1 and 10 are now definite under Section 112, second paragraph, because the range of "about 240 nm to about 280 nm" would be well understood to a person of ordinary skill in the art. Therefore, the Appellant respectfully requests reversal of the rejection of claims 1-3, 7, 9, 10 and 15 under 35 U.S.C. § 112, second paragraph.

C. Section 102(b) Rejection of Claims 1-3, 5-11 and 13-15

1. Legal Standard for Anticipation

The Examiner has the initial burden of factually supporting any prima facie conclusion of anticipation under 35 U.S.C. § 102(b). A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131.

2. The Examiner's Basis

Claims 1-3, 5-11 and 13-15 were rejected under § 102 over Ivanyuta. In making this rejection, the Examiner states "Ivanyuta et al. teach the treatment of the bronchi with 633 nm radiation, which is apparently within the scope of 'about 240 nm to about 280' as evidenced by claims." The Examiner also asserts there is no admonition in Ivanyuta to avoid the treatment of asthmatics with chronic bronchitis.

3. Appellant's Position

a. Meaning of the Cited Reference

Ivanyuta is directed to treating chronic non-obstructive bronchitis. Ivanyuta discloses that disruptions of local and systemic immunity are involved in chronic non-obstructive bronchitis. (Ivanyuta at 1.) Ivanyuta teaches that the efficacy of drugs many not satisfy clinical physicians and that lasers have been proven to affect the pathologic process and immunocompetent cells. (Ivanyuta at 1.) Ivanyuta studied the efficacy of endobronchial low-power laser therapy and its effect on the immune status of patients with chronic non-obstructive bronchitis. (Ivanyuta at 2.) More specifically, Ivanyuta irradiated the mucosa of the trachea and bronchi during fibrobronchoscopy using red light at a wavelength of 633 nm and a power of 6-8 mW at the light-guide exit. (Ivanyuta at 2.) The total dose applied during a session ranged from 2.1-3 J, and four to seven

procedures were performed over a number of days. (Ivanyuta at 2.) Ivanyuta teaches that the patients exhibited the characteristic dynamics of bronchial lesions. (Ivanyuta at 2.) Ivanyuta states that some aggravation occurred after one or two procedures resulting in an initial intensification of coughing and increase of sputum; after an undisclosed time period, the coughing stopped or decreased significantly and the sense of tickling of the throat went away. (Ivanyuta at 3.)

b. Ivanyuta Fails to Disclose or Suggest All of the Features of Independent Claims 1 and 10

The rejection of independent claims 1 and 10 over Ivanyuta is improper because this reference fails to disclose or suggest several features of these claims. Claims 1 and 10, for example, each include "irradiating a length of the airway with a light source having a wavelength of about 240 nm to about 280 nm." Ivanyuta on the other hand teaches irradiating the mucosa of the trachea and bronchi using red light at a wavelength of 633 nm. The wavelength disclosed by Ivanyuta clearly does not anticipate the claimed range of about 240 nm to about 280 nm. The Examiner's basis for this rejection is that dependent claim 5 included red visible light. This was simply an inadvertent error. Claims 1 and 10 were rejected over Ivanyuta in the first Office Action dated 22 August 2007, and in the Amendment dated 31 October 2007 claims 1 and 10 were amended to include the range of "about 240 nm to about 280 nm" to distinguish these claims over Ivanyuta. The Examiner subsequently withdrew the rejection of claims 1 and 10 over Ivanyuta in the Office Action dated 17 March 2008. The Examiner clearly understood the meaning of the claimed range of "about 240 nm to about 280 nm" at that point in time, and his actions in the 17 March 2008 Office Action establish that claims 1 and 10 are not anticipated by Ivanyuta. Therefore, the Appellant respectfully requests reversal of this rejection.

Claims 1, 2, 7 and 9 are further patentable over Ivanyuta because this reference does not teach "a method of treating asthma." As explained above, Ivanyuta discloses

treating only chronic non-obstructive bronchitis. Asthma, on the other hand, is an obstructive pulmonary disease that is completely distinct and different. In the related application on appeal identified in Section II above, the Examiner asserts that Ivanyuta is directed to treating asthma on the grounds that any asthma experienced by Ivanyuta's subjects with chronic non-obstructive bronchitis would have been treated by Ivanyuta's process. Ivanyuta, however, does not mention asthma or that any of his subjects had asthma. As such, Ivanyuta does not disclose that his method would relieve asthma symptoms. The Examiner simply makes up this hypothetical situation and uses it as a basis for the rejection. Therefore, Ivanyuta also fails to anticipate claims 1, 2, 7 and 9 because this reference does not disclose a method for treating asthma.

Ivanyuta further fails to anticipate claims 1, 2, 7 and 9 because Ivanyuta does not teach changing the airway such that a thickness of the airway smooth muscle decreases and bronchoconstriction is reduced. Ivanyuta is completely silent with respect to this feature, and the Examiner does not provide any evidence that Ivanyuta's process would inherently decrease the airway smooth muscle thickness. Ivanyuta, moreover, discloses only a low-power process and it is not clear whether his process would in fact reduce airway smooth muscle thickness. Therefore, Ivanyuta also fails to anticipate this element of claims 1, 2, 7 and 9.

The pending claims are also patentable over Ivanyuta under § 103 because a person of ordinary skill in the art would not irradiate an airway wall of an asthmatic lung to treat asthma based on Ivanyuta. First, Ivanyuta is directed to treating chronic non-obstructive bronchitis such that this reference is not directed to asthma or another chronic obstructive pulmonary disease. Second, Ivanyuta fails to provide any teaching regarding asthma and does not discuss either hypertrophy or hyperplasia. Third, as explained in more detail below, the U.S. Food and Drug Administration understood that airway smooth muscle was important for normal lung function at the time of the present invention. (Declaration of Dr. Michael D Laufer under 37 C.F.R. § 1.132 in the present application, the "Laufer Declaration," at paragraphs 8 and 9.) Fourth, Ivanyuta states

that his procedure caused at least temporary coughing, increased sputum and tickling in the throat that are undesirable in asthma patients. (Ivanyuta at p. 3.) Ivanyuta also stated that further exacerbations of his treatment were intensification of hyperemia of the bronchial mucosa and an increase in secretion in the bronchi lumen. (Ivanyuta at p. 3.) Ivanyuta accordingly would not lead a person of ordinary skill in the art to irradiate an airway wall of an asthmatic lung to treat asthma in light of these factors. Therefore, the pending claims are further patentable over Ivanyuta under §§ 102 and 103.

D. Section 103(a) Rejection of Claims 1-3, 5-11 and 13-15

1. Legal Standard for Obviousness

The Examiner has the initial burden of factually supporting any prima facie conclusion of obviousness under 35 U.S.C. § 103(a), which provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

To reach a proper determination under 35 U.S.C. § 103, "the Examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." MPEP § 2142. Although the tendency to resort to impermissible hindsight based upon the applicant's disclosure is often difficult to avoid, "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." Id.

In *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), the Supreme Court stated that an obvious analysis involves the following:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

More recently, in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), the Supreme Court reaffirmed the holdings of Graham and clarified several aspects of the manner in which obviousness should be determined. First, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results," but "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious" (id. at 1739-40). Second, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art"; rather, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" (id. at 1741). The Court recognized that many significant advances will combine familiar elements: "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known" (id).

Following the decision in *KSR Int'l*, the United States Patent and Trademark Office ("USPTO") issued a memorandum to all Examiners. The memorandum directs Examiners to continue to determine why a person of ordinary skill in the art would make the combination: "in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed" (USPTO Memorandum, *Supreme Court decision on KSR Int'l. Co. v. Teleflex, Inc.*, May 3, 2007, p. 2). Furthermore, it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

Affidavits or declarations, when timely presented, containing evidence of skepticism of experts, etc., must be considered by the Examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. § 103. MPEP § 716.01(a). The weight attached to evidence of secondary considerations will depend upon its relevance to the issue of obviousness and the amount and nature of the evidence. MPEP § 716.01(b). When there is a factually and legally sufficient connection between the objective evidence of non-obviousness and the claimed invention so that the evidence is of probative value in the determination of non-obviousness, it is to be given substantial weight in the obviousness determination. Id. Additionally, "Expressions of disbelief by experts constitute strong evidence of non-obviousness." *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 715 F.2d 693, 698, 216 USPQ 865, 869 (Fed. Cir. 1983) (citing *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 483-484 (1996)); MPEP § 716.05.

2. The Examiner's Basis

Claims 1-3, 5-11 and 13-15 were rejected under 35 U.S.C. § 103(a) over the combination of James, Clarke, Waksman and Regunathan. The Examiner alleges that James teaches the mechanisms involved in airway narrowing in asthma include hypertrophy of smooth muscle; Regunathan teaches that restenosis is a result of hypertrophy of smooth muscle; Waksman teaches the equivalence of irradiation of the intima of bronchi and blood vessels to prevent hyperproliferation; and Clarke teaches that restenosis can be treated by irradiation of a lumen wall with a laser having wavelengths in the claimed ranges to prevent the replication and growth of smooth muscle cells. The Examiner then concludes that because James teaches hypertrophy is one of the mechanisms involved in airway narrowing in asthma, it allegedly would have been obvious to an artisan of ordinary skill to use the method of Clarke for treating asthma on the bases that Waksman teaches bronchial smooth muscle cells and vascular smooth muscle cells are equivalent, and James and Regunathan teach both asthma and restenosis involve hypertrophy of smooth muscle cells. The Examiner

further concludes it allegedly would have been obvious to move the device while irradiating because this would allow longer lesions for the treatment. (21 January 2009 Office Action at p. 10, ln. 12, to p. 11, ln. 2.)

With respect to the Laufer Declaration, the Examiner asserts that this declaration is not per se drawn to the claimed invention. The Examiner, more specifically, asserts that the Laufer Declaration is drawn to the knowledge of one of ordinary skill in the art at the time of the invention with respect to the motivation for combining James, Clarke, Waksman and Regunathan. (21 January 2009 Office Action at p.2, ll. 1-9.)

With regards to paragraphs 8 and 9 of the Laufer Declaration, the Examiner asserts that the facts and conclusions set forth in paragraph 8 are overly broad and that the facts set forth in paragraph 9 are not persuasive because of an alleged lack of context with regard to the method that was analyzed by the FDA. (21 January 2009 Office Action at p. 6, ll. 5-20.) The Examiner asserts that paragraph 10 of the Laufer Declaration merely provides an assertion of what a person of ordinary skill in the art would believe James to teach, and the Examiner dismisses this evidence stating that the rejection is not based on James in isolation. (21 January 2009 Office Action at p. 6, ln. 20 to p.7, ln. 3.) Regarding paragraph 11 of the Laufer Declaration, the Examiner alleges that because James teaches the chronic inflammatory process present in the airway wall of patients is associated with cellular infiltration, deposition of connected tissue, hypertrophy of smooth muscle, goblet cell metaplasia of the epithelium, and an inflammatory exudate containing mucus in the airway movement, "to reverse the chronic inflammatory process would require reversing smooth muscle cell hypertrophy and the excretion of mucus." (21 January 2009 Office Action at p. 7, ll. 4-10.)

With respect to paragraph 14, the Examiner asserts that Dr. Laufer incorrectly states "in all applications, Waksman's invention is directed toward treating an area that has been damaged by an earlier procedure." The Examiner alleges that Waksman can be construed to refer to treating uninjured tissue on the basis that Waksman at page 7,

ln. 36 to p. 8, ln. 1, teaches "it should be noted that the method of the present invention may be carries [sic] before during or after an angioplasty or other artery opening procedure." The Examiner further alleges that Waksman can be construed to treat mucus glands in the case of treating bronchi on the basis that Waksman at p. 5, ll. 8-13, states "the treating elements may be used to treat the intraluminal passageway through which they are delivered or may be used to treat a surrounding area of the body located within a maximum radius of the intraluminal passageway through which they are delivered."

With respect to paragraph 15, the Examiner asserts that hypertrophy can include hyperplasia on the grounds that the definition of hyperplasia in Stedman's Medical Dictionary, 26th Edition, is "an increase in the number of cells in a tissue or organ, excluding tumor formation, whereby the bulk of the part or organ may be increased. SEE ALSO, hypertrophy." (21 January 2009 Office Action at p. 7, ln. 21 to p. 8, ln. 6.) The Examiner further asserts that hypertrophy can include hyperplasia on the basis that James allegedly states both the production of connected tissue and smooth muscle cell hypertrophy are separate consequences of the inflammatory process which is to be reversed. (21 January 2009 Office Action at p. 8, ll. 6-10.) The Examiner then equates hyperplasia with hypertrophy for combining the method of Clarke with James.

With regard to paragraph 16 of the Laufer Declaration, the Examiner dismisses Dr. Laufer's statement that a person of ordinary skill in the art would not apply the methods of Clarke, Waksman and Regunathan to treat uninjured airway smooth muscle tissue on the grounds that James refers to a purported hyperplasia meaning of the term hypertrophy and Waksman teaches applying his treatment to uninjured tissue. (21 January 2009 Office Action at p. 8, ll. 10-14.) With respect to paragraph 18 in the Laufer Declaration, the Examiner dismisses Dr. Laufer's statement that the increase in airway thickness in asthma is due to hypertrophy, rather than hyperplasia, on the grounds that this statement is not convincing in view of the Examiner's reading of James; the Examiner similarly dismisses the statements in paragraph 19 of the Laufer

Declaration as being based on an erroneous interpretation of James. (21 January 2009 Office Action at p. 8, ll. 15-20.)

With respect to paragraph 21, the Examiner asserts that the basis for Dr. Laufer's statement that "a person of ordinary skill in the art would not be motivated or otherwise think of applying radiation to affect a change in the airway mucus gland cells such that mucus secretions of the airway are reduced" is unclear. The Examiner asserts that Dr. Laufer discusses only the lack of teaching of injuring smooth muscle cells in the bronchi, and that there is no discussion of a desire of preserving mucus glands.

3. Appellant's Position

a. The Laufer Declaration

The Examiner's assessment of the Laufer Declaration is replete with errors including several instances where the Examiner substitutes his erroneous readings of the prior art for Dr. Laufer's knowledge as a person skilled in the art at the time of the invention. The Laufer Declaration should be given significant patentable weight even though Dr. Laufer is an interested party because it is supported by extrinsic evidence and Dr. Laufer has been a person of ordinary skill in the art since before 1998. The Laufer Declaration should also be given significant patentable weight because it is indeed drawn to the claimed subject matter and, more particularly, the faults in the Examiner's interpretations of the references and conclusions. Evidence submitted in a declaration depends on the relevance to the issue of obviousness, and there is a sufficient nexus between the merits of the claimed invention and the evidence of secondary considerations when the evidence is of probative value in the obviousness determination. MPEP § 716.01(b).

Claim 1 is directed to a method for treating asthma by selecting an airway that has hypertrophied airway smooth muscle. The selected airway is irradiated with a light source having a wavelength of about 240 nm to about 280 nm and at an intensity which

causes a change in the airway such that a thickness of the airway smooth muscle decreases and bronchoconstriction of the airway is reduced. One feature of claim 1 is accordingly debulking existing, uninjured smooth muscle tissue in an asthmatic lung in addition to preventing future replication of the lung tissue. Claim 10 is also directed to a method for treating asthma by irradiating the airway with light having a wavelength of about 240 nm to about 280 nm. Claim 10 further includes that the intensity of the radiation causes a change in mucus glad cells that reduces mucus secretions.

The Laufer Declaration provides evidence that is probative to the obviousness determination because, *inter alia*, it provides extrinsic evidence that teaches away from decreasing airway smooth muscle thickness. For example, the Examiner states James' teaching of the reversal of the chronic inflammatory process "would require reversing smooth muscle hypertrophy." (21 January 2009 Office Action at p. 7, ll. 4-10.) The Laufer Declaration, however, establishes that James teaches many different mechanisms and areas of chronic asthmatic inflammation, but it does not require the reversal of any specific mechanism. (Laufer Declaration at paragraph 7.) The Laufer Declaration also establishes that James does not teach causing a change in mucus gland cells, and that the United States Food and Drug Administration (USFDA) was so skeptical of debulking airway smooth muscle that it denied approval of doing so until 2005. (Laufer Declaration at paragraphs 7 and 9.) The Laufer Declaration also directly refutes several other assertions and unsupported conclusions concocted by the Examiner. Therefore, the Laufer Declaration provides highly probative evidence regarding the obviousness determination and should be accorded significant weight.

The Examiner erred in asserting that the Laufer Declaration is not per se drawn to the claimed invention. More specifically, the Examiner stated "the Laufer Declaration is not per se drawn to the claimed invention (as it only discusses a subset of the claimed invention wherein all smooth muscle cells are actually killed (see the Laufer Declaration at paragraph 8, last sentence)[])." (21 January 2009 Office Action at p. 2, ll. 6-9.) In contrast to the Examiner's position, the last sentence of paragraph 8 of the

Laufer Declaration is not limited to situations where all smooth muscle cells are killed, but rather this sentence reads: "Therefore, in 1998, a person of ordinary skill in the art would have understood that airway smooth muscle had a functional purpose and that airway smooth muscle cells should not be killed." Nothing in the last sentence of paragraph 8 of the Laufer Declaration describes a situation that is limited to killing all of the airway smooth muscle cells. The Laufer Declaration establishes, *inter alia*, that a person skilled in the art at the time of the invention would have understood that airway smooth muscle cells should not be killed to the extent that the lack of larger airway smooth muscle tone could impede the functional purpose that airway smooth muscle was thought to perform in normal lung function at the time of the invention (see, e.g., paragraphs 8 and 9 of the Laufer Declaration). The Laufer Declaration accordingly discusses the understanding of a person skilled in the art at the time of the invention regarding the controversy surrounding the destruction or removal of airway smooth muscle as covered by the "decreasing airway smooth muscle thickness" element of claim 1 or the "mucus gland" element of claim 10. Thus, the Laufer Declaration is per se drawn to the claimed invention.

The Examiner also erred in dismissing the statement that the prevailing view at the time of the invention was airway smooth muscle had a functional purpose. Paragraph 8 of the Laufer Declaration cites two independent articles that show the early body of literature dating back over 125 years taught airway smooth muscle had one or more functional purposes. Dr. Laufer states "Although Mitzner cites later articles as refuting some of the functional purposes of airway smooth muscle, Mitzner also points out that other listed functional purposes were still thought to be valid as late as 2004 (e.g., peristalsis to assist exhalation)." (Laufer Declaration at paragraph 8.) Thus, Dr. Laufer's statement that "a person of ordinary skill in the art would have understood that airway smooth muscle had a functional purpose as of 1998" is fully supported by the cited articles. Moreover, as a doctor in the field at that time, Dr. Laufer's statement is uncontested by any factual evidence presented by the Examiner.

The Examiner further erred with respect to paragraph 8 of the Laufer Declaration in stating that the Laufer Declaration "would seem to indicate that one of ordinary skill in the art would believe that not even the death of a single airway smooth muscle cell could be tolerated, however, the instant claims are of such breadth that they would read on a procedure where only a small number of cells are killed." (21 January 2009 Office Action at p. 6, ll. 5-10.) In contrast to the Examiner's statement, the Laufer Declaration does not state that a person of ordinary skill in the art at the time of the invention would have believed that not even the death of a single airway smooth muscle cell could be tolerated. The Laufer Declaration consistently states "a person of ordinary skill in the art would have understood that airway smooth muscle had a functional purpose and that airway smooth muscle cells should not be killed." (Emphasis added.) Dr. Laufer clearly used the plural term "cells" in direct opposition to the Examiner's unfounded assertion. Moreover, it is clear from paragraphs 8 and 9 of the Laufer Declaration that Dr. Laufer addressed the situation of decreasing airway smooth muscle thickness where more than a single muscle cell was killed.

Paragraph 9 of the Laufer Declaration establishes that experts were skeptical about decreasing airway smooth muscle tissue at the time of the invention. More specifically, irrespective of the methodology for decreasing airway smooth muscle thickness, the USFDA did not grant Asthmatx, Inc. approval to treat asthma in a human patient by debulking airway smooth muscle tissue using RF energy or any other modality until 2005. The redacted portion of a letter from James E. Dillard, III, director of the Division of Cardiovascular and Respiratory Devices in the Office of Device Evaluation of the United States Food and Drug Administration, reads:

> Of concern is that ablation of airway smooth muscle and small bronchi may have negative effects by preventing airway dilation during sympathetic stimulation, e.g., during exercise. Patients could conceivably continue to have asthma attacks with secretions and smaller airway broncospasm and then be unable to effectively cough and clear these secretions due to lack of larger airway smooth muscle tone. Reduced smooth muscle support of the conducting airways,

coupled with underlying asthma, could lead to complications such as bronchiectasis.

The quoted language from Mr. Dillard stands for the proposition that the "lack of larger airway smooth muscle tone" (i.e., the airway smooth muscle tissue with decreased thickness) and the concomitant "reduced smooth muscle support of the conducting airways" associated with the debulking could lead to undesirable complications. Mr. Dillard took the position that airway smooth muscle has a functional purpose (e.g., dilation and restriction), and that it should not be reduced in size. The Examiner dismissed this evidence on the grounds that there was no context of the device or method that the USFDA analyzed and thus it was "impossible" to draw an inference of the knowledge of a person skilled in the art. The Examiner misses the point of paragraph 9 of the Laufer Declaration and the excerpt from the USFDA letter. The point is this: The premier U.S. Government Agency on the topic believed (a) that airway smooth muscle was thought to perform an important function and (b) it would be undesirable to reduce the size of airway smooth muscle in asthma patients irrespective of the energy modality. Therefore, paragraph 9 of the Laufer Declaration and the excerpt from the USFDA should be given considerable weight.

Paragraph 10 of the Laufer Declaration establishes that James teaches the increase in airway wall thickness associated with asthma is not confined to the airway smooth muscle, but rather inflammation of the submucosa and the epithelium as well. This is directly from James and is incontrovertible. (James at p. 245, col. 1.) Paragraph 10 of the Laufer Declaration also establishes that James does not teach any specific mechanism to reverse the inflammatory progression in the airway wall. Although James teaches the inflammatory process should be reversed, James also teaches that there are many other causes of the inflammatory process besides smooth muscle hypertrophy and the inflammation is in other areas than the smooth muscle. (See, e.g., James at p. 245, col. 2, and p. 246, col. 1.) James does not teach which of the several listed causes should be treated to reverse the inflammation. Therefore, in light of the

evidence from paragraphs 8 and 9 of the Laufer Declaration, Dr. Laufer correctly summarizes that a person skilled in the art would not understand James to mean that asthma should, or then could, be treated by debulking the airway smooth muscle as opposed to reversing any of the other causes or areas of inflammation set forth by James.

Paragraph 14 of the Laufer Declaration states that Waksman discloses an apparatus for delivering radioactive treatment from a radionuclide to tissue that has been damaged. Waksman teaches that a healing process in response to an injury is an overgrowth of tissue caused by increased cell proliferation that renarrows the lumen, and in particular Waksman teaches applying radiation from a radionuclide to prevent or inhibit hyperplasia following a balloon angioplasty procedure. (Waksman at 1:17-20, 5:13-18 and 6:19-25, emphasis added.) Although Waksman provides a long list of vascular applications and a list of non-vascular applications, including the bronchi and lungs, in which his invention may be used, in all of these applications Waksman's invention is directed toward treating an area that has been damaged by an earlier procedure or by inhibiting the proliferation of additional cells. (Waksman at 5:18-6:5.) The Examiner asserts that Waksman is directed toward applying his treatment to uninjured tissue on the grounds that Waksman states that his method may be carried out before, during or after an angioplasty or other artery-opening procedure. (Waksman at p. 7, ln. 36 to p. 8, ln. 1.) A person skilled in the art, however, would not read Waksman so expansively because vascular smooth muscle provides an essential function for maintaining blood pressure such that a person skilled in the art would not apply the method taught by Waksman in a manner that would debulk existing uninjured vascular smooth muscle tissue. (Laufer Declaration at paragraph 16.)

Paragraph 15 of the Laufer Declaration states that restenosis in vascular structures is caused by hyperplasia as opposed to hypertrophy of smooth muscle cells. Additionally, Dr. Laufer states hyperplasia in vascular applications is the excessive proliferation of new or additional cells above the level of normal cell production, whereas

hypertrophy is the increase in size of existing cells without necessarily increasing the number of cells above normal levels. In contrast to the Examiner's assertion the difference between hyperplasia and hypertrophy is further supported by the definitions of these terms in Stedman's Medical Dictionary, 27th Edition (2000). Although the Examiner's quote of Stedman's definition of hyperplasia is accurate, the Examiner read "SEE ALSO hypertrophy" as being synonymous. This is incorrect. Stedman's defines hypertrophy as a "general increase in bulk of a part or organ, not due to tumor formation. Use of the term may be restricted to denote greater bulk through increase in size, but not in number of cells or other individual tissue elements." Stedman's accordingly supports defining hyperplasia and hypertrophy as two distinct mechanisms such that hypertrophy does not include hyperplasia. Moreover, James consistently uses the terms hyperplasia and hypertrophy separately to mean separate conditions.

With regard to paragraph 16 of the Laufer Declaration, Dr. Laufer correctly states that neither Regunathan nor Clarke nor Waksman teaches debulking or otherwise removing uninjured vascular smooth muscle tissue that existed before an injury. All of these references are clear that the restenosis, or renarrowing of a lumen, treated by their methods is caused by hyperproliferation. Dr. Laufer also notes that vascular smooth muscle provides an essential function for maintaining blood pressure through vasoconstriction and vasodilation such that a person skilled in the art would not apply the methods taught by Regunathan or Clarke in a manner that would debulk existing vascular smooth muscle tissue.

b. Meaning of the Cited References

James describes mechanics of airway narrowing in asthma patients. James teaches that the airway walls of asthma patients are thickened by chronic inflammation and concludes that such thickening of the airway walls could be as important as smooth muscle shortening in determining the airway responsiveness of these patients. (James at Summary.) James indicates that the airways of the asthmatic patients showed

infiltration with inflammatory cells, thickening of the basement membrane, mucous gland and goblet cell prominence, and partial occlusion of the lumen with mucus and cellular debris. (James at p. 243, col. 3.) In addition, James discloses marked folding of the epithelium in some airways with a prominent circular layer of muscle. (James at p. 243, col. 3 to 244, col. 1.) The increase in wall thickness, therefore, is not confined to the airway smooth muscle, but rather it also includes the submucosa and epithelium. (James at p. 245, col. 1.) James, for example, teaches that the chronic inflammatory process present in the airway wall in patients with asthma is associated with (a) cellular infiltration, (b) deposition of connective tissue, (c) goblet cell metaplasia of the epithelium, and (d) an inflammatory exudate containing mucus in the airway lumen in addition to hypertrophy of smooth muscle. (James at p. 246, col. 1.) James further teaches that an important feature of asthma treatments at that time was the rapid reversibility of airway obstruction with drugs that relax smooth muscle. (James at p. 245, col. 3.) According to James, bronchodilation does not need to be limited to reversal of excessive smooth muscle contraction, but rather reversing the muscle contraction can also be applied for non-excessive muscle contraction of thickened airway walls to increase airway caliber and lower the resistance to a similar degree. (James at p. 245, col. 3.) Based on these findings, James concludes that changes produced by chronic inflammatory processes can lead to excessive airway narrowing without excessive smooth muscle contraction such that the treatment of asthma should focus on (a) reversing the inflammatory changes in the airway wall and (b) relaxation of the airway smooth muscle. (James at p. 246, col. 1.)

Regunathan discloses that vascular hyperplasia, i.e., the excessive proliferation and hypertrophy of vascular smooth muscle cells, is a major pathogenic mechanism contributing to vascular pathology in atherosclerosis, hypertension resulting from renal artery stenosis and other causes, restenosis of coronary and other arteries after coronary angioplasty, insertion of vascular stents, and other conditions. (Regunathan at 1:17-27.) The invention of Regunathan is directed to a non-invasive method of

inhibiting the initiation or progression of vascular hyperplasia and, in particular, to inhibiting proliferation of vascular smooth muscle cells. (Regunathan at 1:34-37.) Regunathan, more specifically, teaches a method of inhibiting the proliferation of vascular smooth muscle cells by administering a vascular smooth muscle cell anti-proliferative effective amount of an I_2 imidazoline receptor agonist. (Regunathan at 1:37-42.)

Clarke is directed toward inhibiting restenosis associated with angioplasty and teaches that intimal hyperplasia or proliferation of vascular smooth muscle cells is a major factor in restenosis. (Clarke at 1:1-5 and 1:41-43.) Clarke further teaches vascular smooth muscle cells enter their growth cycle 2-3 days after injury and the majority of the vascular smooth muscle cells cease to proliferate within 7 days after injury. (Clarke at 1:43-50.) Clarke indicates that the total number of smooth muscle cells reaches a peak about two weeks after injury and remains constant for up to one year; Clarke states this suggests that a reduction of the number of smooth muscle cells injured during angioplasty will reduce the likelihood of subsequent restenosis. (Clarke at 1:50-55.) To inhibit restenosis, Clarke teaches reducing the proliferation of additional vascular smooth muscle cells in the blood vessel walls at an angioplasty site by irradiating the angioplasty site with the appropriate radiation in the UV wavelength range. (Clarke at 2:39-44.) The irradiation kills a major portion of the injured smooth muscle cells in the media so that few, if any, smooth muscle cells remain in the angioplasty site to proliferate and cause restenosis. (Clarke at 5:1-9.) However, as shown in Figures 3B and 3C, the thickness of media is not reduced by the process.

Waksman discloses an apparatus for delivering radioactive treatment from a radionuclide to tissue that has been damaged. Waksman teaches that the healing process in response to an injury is an overgrowth of tissue caused by increased cell proliferation that renarrows the lumen. (Waksman at 1:17-20.) In particular, Waksman teaches applying radioactive radiation from a radionuclide to prevent or inhibit hyperplasia following a balloon angioplasty procedure. (Waksman at 5:13-18 and 6:19-

25.) Waksman provides a long list of vascular applications and also a list of non-vascular applications, including the bronchi in lungs, in which his invention may be useful. (Waksman 5:18-6:5.) However, in all of the applications disclosed in Waksman, his invention is directed toward inhibiting the proliferation of additional cells at an area that has been injured during an earlier procedure. Waksman, moreover, does not disclose anything with respect to mucus or mucus gland cell debulking.

c. Claim 1 – A Person of Ordinary Skill in the Art at the Time of the Invention Would Not Have Applied the Method of Clarke in an Asthmatic Lung For Treating Asthma Nor Have Understood That It Would Have Been Obvious to Try the Method of Clarke in Such a Manner Based on James, Waksman and Regunathan

The rejection of claim 1 over the combination of James, Clarke, Waksman and Regunathan is improper because the Examiner incorrectly concludes that James' teachings require the reversal of airway smooth muscle hypertrophy and that the teachings of the other references would lead a person of ordinary skill in the art to apply the method in Clarke to reverse inflammation of airway smooth muscle to treat asthma. James teaches that the chronic airway inflammation of asthma is associated with several different factors including (a) cellular infiltration, (b) deposition of connective tissue, (c) goblet cell metaplasia of the epithelium, (d) hypertrophy of smooth muscle, and (e) an inflammatory exudate containing mucus in the airway lumen. (James at p. 246, column 1.) James further teaches that the inflammation occurs in several areas including the airway smooth muscle, the epithelium and the submucosa. (James at p. 245, column 1.) James concludes that the treatment should focus on both (a) reversing the inflammatory changes in the airway wall and (b) relaxation of the airway smooth muscle, but James does not teach which specific causes of the inflammation or which specific areas of the inflammation should be treated. (James at p. 246, column 1.) James, moreover, does not teach or otherwise suggest anything regarding how any of the listed causes should be treated other than drug treatments. James clearly does not teach any mechanism to debulk airway smooth muscle tissue.

(Laufer Declaration at paragraph 10.) Therefore, to support this rejection, the Examiner must show (a) that a person skilled in the art in 1998 would select debulking airway smooth muscle as the mechanism to reverse the chronic inflammation taught by James, and (b) that Clarke's process would be used for debulking uninjured, hypertrophied airway smooth muscle.

The Examiner fails to establish that a person skilled in the art at the time of the invention would have selected decreasing airway smooth muscle thickness to treat asthma. The Examiner uses only James for the proposition that a person skilled in the art would in fact reduce airway smooth muscle mass for treating asthma. However, the prevailing view at the time of the invention was that airway smooth muscle tissue performed an important functional purpose for normal lung function and that decreasing airway smooth muscle thickness could impair the normal lung function in an asthmatic lung. For example, the USFDA believed that airway smooth muscle facilitated airway dilation such that the lack of airway smooth muscle tone caused by decreasing airway smooth muscle thickness could render asthma patients unable to cough or clear secretions during exercise or other sympathetic stimulation. (Laufer Declaration at paragraph 9 citing USFDA letter dated 16 February 2001 regarding IDE no. G010016.) This was the reason why the USFDA initially denied approval of an Asthmatx device that reduced the airway smooth muscle tone (i.e., decreased the airway smooth muscle thickness) via ablation. Notably, the USFDA was not concerned about the mechanism (e.g., ablation), but rather the concern was the reduction in smooth muscle tone. Also, Paragraph 8 of the Laufer Declaration provides factual evidence that other experts in the art recognized that airway smooth muscle tissue performed a functional purpose for normal lung function. This evidence accordingly establishes that third party experts in the field at the time of the invention thought that airway smooth muscle performed an important functional purpose, and that airway smooth muscle thickness should not be decreased for fear of further impairing lung function in an asthmatic patient. Therefore,

there is significant evidence that a person skilled in the art would not select decreasing airway smooth muscle thickness even in light of James' teachings.

The Examiner erred by completely dismissing the statement from the USFDA on the grounds that it purportedly lacked any context with regard to the claimed method. The Examiner is incorrect and misses the point - the USFDA's statement is highly probative because it establishes that the foremost U.S. Government Agency in the field was skeptical about decreasing airway smooth muscle thickness to treat asthma at the time of the invention. The statement from the USFDA regarding the size and tone of airway smooth muscle is not only directly on point, but it comes from a government agency that has far more expertise in the relevant art than the Examiner. The articles cited in paragraph 8 of the Laufer Declaration further support the view that airway smooth muscle was thought to perform an important function at the time of the invention. Therefore, in light of all the evidence to the contrary, the Examiner's assertion that in 1998 a person skilled in the art would consider reducing airway smooth muscle to be a medically acceptable option for treating asthma is incorrect.

The Examiner also fails to establish that Clarke's process for preventing excessive growth of new cells in response to a vascular injury would be used to debulk uninjured, hypertrophied airway cells. To reach this conclusion, the Examiner argues that hypertrophy can include hyperplasia and that James uses the terms hypertrophy and hyperplasia interchangeably. The Examiner's analysis, however, does not comport with the use of hyperplasia and hypertrophy set forth in either the cited references, Stedman's Medical Dictionary (27th Edition), or the understanding of a person of ordinary skill in the vascular space. Starting with Regunathan, although this reference states that "vascular hyperplasia, i.e., the excessive proliferation and hypertrophy of VSM cells" is a major pathogenic mechanism contributing to vascular pathology in restenosis, Regunathan describes treating disorders by administering a vascular smooth muscle anti-proliferative pharmacological agent. (Emphasis added.) The treatment described in Regunathan is accordingly directed to limiting excessive

proliferation of vascular cells (i.e., hyperplasia) as opposed to reducing the preexisting size of the VSM cells (i.e., hypertrophy). (Laufer Declaration at paragraph 12.) These terms are not interchangeable in the vascular space, and the Examiner cannot be allowed to pick and chose from an inaccurate usage of these terms. Therefore, Regunathan does not teach reducing the size of existing, uninjured smooth muscle cells (i.e., hypertrophy).

Clarke is also directed toward inhibiting restenosis associated with hyperplasia caused by a vascular injury (i.e., by reducing the proliferation of additional vascular smooth muscle cells). (Laufer Declaration at paragraph 13.) Clarke does not mention hypertrophy, but instead uses hyperplasia to mean the proliferation of new smooth muscle cells in response to an injury. As such, based on the entire teachings of Clarke and Regunathan, a person skilled in the art at the time of the invention would have understood that the purpose of both Regunathan and Clarke was to inhibit the production of additional vascular smooth muscle cells that would normally incur in response to damage, injury or other trauma to the vessel wall. (Laufer Declaration at paragraph 15.)

James consistently states that the chronic inflammation associated with asthma is caused by several factors including "smooth muscle hypertrophy." James mentions hyperplasia in the context of citing an article by Heard and Hosain stating "Heard and Hosain (9) showed that this [increase in smooth muscle in the major bronchi] was due to hyperplasia rather than hypertrophy. The present study confirms an increase in smooth muscle volume as well as an increase in the volume of the nonmuscular wall components." The Heard and Hosain article clearly distinguishes between hyperplasia and hypertrophy. James merely states that his study confirms an increase in smooth muscle volume, but James did not confirm that the cause was hyperplasia. Instead, James consistently stated that the increase in smooth muscle volume was caused by hypertrophy. Given that Heard and Hosain were clear that these terms have different meanings and that James consistently used only hypertrophy, the best reading of

James to a person skilled in the art is that James used hypertrophy to refer to a different condition than hyperplasia.

In putting the teachings of these references together, it accordingly starts with James' teaching that the chronic inflammation associated with asthma is caused, in part, by smooth muscle hypertrophy. This type of tissue growth is different than the growth caused by proliferation of new cells. For example, unlike a proliferation of new cells in response to an injury, enlargement of uninjured preexisting cells is caused by use (e.g., muscle growth through exercise). Neither Regunathan nor Clarke teaches decreasing the thickness or otherwise reducing uninjured vascular smooth muscle tissue that existed before an injury or other trauma occurred. Therefore, a person of ordinary skill in the art would not use Clarke's method to irradiate an uninjured airway wall of an asthmatic lung at a wavelength and intensity that, over time, would decrease airway smooth muscle thickness based on the teachings of James, Regunathan, Clarke or Waksman either individually or collectively. (Laufer Declaration at paragraph 19.)

The addition of Waksman to the combination of James, Regunathan and Clarke does not provide the missing elements from James, Regunathan or Clarke. The Examiner sites Waksman for the proposition that this reference teaches irradiating blood vessels is equivalent to irradiating the intima of bronchi to prevent hyperproliferation. (21 January 2009 Office Action at p. 11, ll. 15-16.) This assertion by the Examiner is incorrect because vascular structures and airway structures are significantly different from each other. For example, the airway epithelium is comprised of tight junctions of columnar cells that are 10-15 times thicker than the single flat layer of squamous cells that comprise the vascular endothelium. (Laufer Declaration at paragraph 20.) The airway epithelium also necessarily facilitates diffusion of nitrogen for proper lung function, but the vascular endothelium prevents diffusion of nitrogen and nitrogen-containing substances (e.g., nitrogen monoxide in particular) because these gases have a direct effect on causing vascular smooth muscle to contract. (Laufer Declaration at paragraph 20.) The prevention of diffusion of nitrogen and nitrogen-

containing substances could be catastrophic in an airway. (Laufer Declaration at paragraph 20.) The airway epithelium and blood vessel endothelium are accordingly two different materials with different properties that react differently to irradiation. As a result, the intensity of UV radiation to prevent the hyperproliferation of vascular smooth muscle cells in response to angioplasty in a blood vessel does not inherently debulk uninjured airway smooth muscle through the epithelium of an airway. (Laufer Declaration at paragraph 20.) The broad assertion that Waksman teaches irradiating the intima of bronchi is equivalent to irradiating blood vessels to prevent hyperproliferation is accordingly incorrect. Therefore, the addition of Waksman does not overcome the shortcoming of the combination of James, Clarke and Regunathan.

Moreover, even if Waksman arguably teaches equivalence between irradiating the intima of bronchi and irradiating blood vessels to prevent hyperproliferation in response to an injury using a radionuclide, Waksman still does not teach any equivalence between irradiating uninjured vascular or airway smooth muscle tissues using light at a wavelength of about 240 nm to about 280 nm. Waksman teaches the use of radioactive radiation from a radionuclide to prevent hyperproliferation of new cells. The Examiner does not provide any teaching that Waksman's radioactive radiation from a radionuclide would inherently have the same effect as the claimed wavelength range on either airway or vascular smooth muscle. A person of ordinary skill in the art at the time of the invention accordingly would not consider Waksman to teach a reason to irradiate an uninjured airway wall of an asthmatic lung at a wavelength of about 240 nm to about 280 nm and intensity that, over time, would debulk airway smooth muscle. Therefore, even when combined, the cited combination of references fails to teach all of the claimed elements.

d. Claim 10 – Even If the References are Properly Combined, Which the Appellant Does Not Concede, the Cited Combination of References Does Not Teach All of the Elements of Claim 1

Claim 1 is patentable over the cited combination of references because none of these references teaches a process that decreases the thickness of uninjured hypertrophied airway smooth muscle tissue. As noted above, Regunathan, Clarke and Waksman only teach methods for inhibiting the proliferation of additional smooth muscle cells that occurs in response to a vascular injury. (Laufer Declaration at paragraph 16.) Vascular smooth muscle, moreover, provides an essential function for maintaining blood pressure through vasoconstriction and vasodilation. (Laufer Declaration at Paragraph 16.) A person skilled in the art, therefore, would not apply the methods taught in Regunathan, Clarke and/or Waksman in a manner that would decrease the thickness of existing vascular smooth muscle tissue because this would reduce the smooth muscle tone. (Laufer Declaration at paragraph 16.) The rationale supporting Dr. Laufer's statement is similar to the rationale that the USFDA used to initially deny approval of Asthmatx's device because vascular smooth muscle incontrovertibly performs an essential purpose. If a person of ordinary skill in the art would not apply the method taught by Clarke to treat uninjured hypertrophied vascular smooth muscle, then if follows that Clarke would not be applied to treat uninjured hypertrophied airway smooth muscle. As a result, if the cited references were combined and applied as set forth in the references, the resulting process would irradiate the airway smooth muscle at a wavelength and intensity that merely prevents the future proliferation of smooth muscle cells after an injury instead of debulking the existing uninjured smooth muscle tissue. The cited combination of references, therefore, fails to disclose or suggest all the features of claim 1.

e. Claim 10 – Even if the References are Properly Combined, Which the Appellant Does Not Concede, the Cited Combination of References Do Not Teach All of the Elements of Claim 10

Claim 10 was also rejected under Section 103 over the combination of James, Clarke, Waksman and Regunathan. Claim 10 is directed toward treating asthma by irradiating an airway in the lung at a wavelength of about 240 nm to about 280 nm. Claim 10 also includes that the irradiation is at an intensity which causes a change in airway mucus gland cells such that mucus secretions of the airway are reduced. None of the cited references teaches irradiation of the airway at a wavelength of about 240 nm to about 280 nm that changes airways such that mucus secretions of the airway are reduced. Neither Clarke nor Waksman nor Regunathan teaches that radiation at a wavelength of about 240 nm to about 280 nm achieves this result. Although Waksman teaches that his radionuclide can be used to irradiate the bronchi and the lungs, his invention is directed toward preventing or inhibiting hyperplasia instead of changing mucus gland cells in the airways. The radiation from a radionuclide, moreover, is radioactive radiation at a much smaller wavelength than the claimed range of about 240 nm to about 280 nm. Therefore, it is not inherent that Waksman's radiation will produce the same results as the claimed range. Claim 10 is accordingly patentable over the combination of James, Clarke, Waksman and Regunathan under Section 103 because this combination of references fails to disclose at least this feature of claim 10.

E. Obviousness-Type Double Patenting Rejections

1. The Examiner's Position

Claims 1 and 10 were rejected under the doctrine of obviousness-type double patenting over the claims of U.S. Patent Nos. 7,027,869, 6,634,363, 6,411,852, 6,299,633, 6,283,989, 6,283,988, 6,200,333, 6,083,255, 6,273,907, and 5,972,026. Claims 1 and 10 were also rejected under the doctrine of provisional obviousness-type double patenting over the claims of co-pending U.S. Application Nos. 11/608,606,

11/562,925, 11/398,353, 11/408,668, 11/420,442, 11/361,564, 11/117,905, 11/617,512, 11/614,914, and 11/534,621.

Claims 1-3, 5-11 and 13-15 were rejected under the doctrine of obviousness-type double patenting over the claims of U.S. Patent Nos. 6,488,673, 7,264,002, and 7,273,055. Claims 1-3, 5-11 and 13-15 were also rejected under the doctrine of provisional obviousness-type double patenting over the claims of co-pending U.S. Application Nos. 11/614,919, 11/612,620, 11/618,533, 11/609,242, 11/425,345, 11/421,444, and 11/562,910.

2. The Appellant's Position

The rejection of claims 1-3, 7, 9, 10 and 15 over the issued U.S. patents listed above is now moot because the Appellant filed Terminal Disclaimers in the Amendment dated 21 May 2009 regarding the following U.S. Patent Nos.: 5,972,026; 6,083,255; 6,200,333; 6,273,907; 6,283,988; 6,283,989; 6,299,633; 6,634,363; 6,411,852; 6,488,673; 7,027,869; 7,264,002; and 7,273,055. According to the Patent Application Information Retrieval system, these Terminal Disclaimers were accepted on 25 June 2009.

The provisional rejection of the pending claims over the later filed U.S. Patent Application Nos.: 11/608,606, 11/562,925, 11/398,353, 11/408,668, 11/420,442, 11/361,564, 11/117,905, 11/617,512, 11/614,914, 11/534,621, 11/614,919, 11/612,620, 11/618,533, 11/609,242, 11/425,345, 11/421,444, and 11/562,910 will be mooted if the present application is allowed to issue. The present application antedates all of the foregoing copending applications, and thus pursuant to MPEP § 804 the present application should not be subject to an obviousness-type double patenting rejection over those applications if it is in condition for allowance before issuance of the listed copending applications. The Appellant respectfully requests reversal of this rejection if the other rejections set forth above are reversed.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A include the amendments filed by Applicant on 22 July 2008.

Dated: 21 August 2009

Respectfully submitted,

By _____

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APPENDIX A

Claims Involved in the Appeal of Application Serial No. 10/810,276

1. (Previously presented) A method of treating asthma, comprising:

selecting an airway for treatment, wherein the airway has hypertrophied airway smooth muscle;

irradiating a length of the airway with a light source having a wavelength of about 240 nm to about 280 nm and an intensity which causes a change in the airway such that a thickness of the airway smooth muscle decreases and bronchoconstriction of the airway is reduced.

2. (Previously presented) The method of claim 1, where the change in the airway occurs in smooth muscle cells.

3. (Previously presented) The method of claim 1, where the change in the airway occurs in mucus gland cells.

4. (Canceled)

5. (Canceled)

6. (Canceled)

7. (Original) The method of claim 1, further comprising moving the light source along the airway.

8. (Canceled)

9. (Previously presented) The method of claim 1, where the change in the airway comprises preventing airway cells from replicating.

10. (Previously presented) The method of controlling mucus within a lung, comprising:

selecting an airway for treatment;

irradiating a length of the airway with a light source having a wavelength of about 240 nm to about 280 nm and an intensity which causes a change in airway mucus gland cells such that mucus secretions of the airway are reduced.

11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Original) The method of claim 10, further comprising moving the light source along the airway.

APPENDIX B

A copy of evidence pursuant to §§ 1.130, 1.131, or 1.132 and/or evidence entered by or relied upon by the examiner that is relevant to this appeal is attached hereto. A Declaration Under 37 C.F.R. § 1.132 of Dr. Michael D. Laufer was entered in the present application in the 21 January 2009 Office Action.

Declaration Under 37 C.F.R. § 1.132 of Dr. Michael D. Laufer in the present application.

Attachment 1

Declaration of Michael D. Laufer, M.D., Under 37 C.F.R. 1.132

Docket No.: 649218008US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	MICHAEL D. LAUFER	
APPLICATION NO.:	10/810,276	CONFIRMATION NO.: 8525
FILED:	MARCH 26, 2004	ART UNIT: 3735
FOR:	METHOD FOR TREATING AIRWAYS IN THE LUNG	EXAMINER: D. M. SHAY

Declaration of Michael D. Laufer, M.D., Under 37 C.F.R. 1.132

I, Michael D. Laufer, M.D., hereby declare and state.

1. I received a Bachelor of Arts degree from the University of Colorado at Boulder in 1980, and I received a Medical Doctorate degree from the Stanford University School of Medicine in 1985. My postdoctoral training included the following positions: Intern in Emergency Medicine at Harbor-UCLA from 1985-1986; Resident in Emergency Medicine at Harbor-UCLA from 1986-1988; and Fellow/Attending in Trauma, Surgery, Emergency Medicine and Pre-Hospital Care at Stanford University from 1988-1989.

2. I hold the following licenses and certifications:

   1983 Advanced Cardiac Life Support Instructor and Provider
   1983 Basic Life Support Instructor and Provider
   1986 Advanced Trauma Life Support Provider and Course Instructor
   1986 Basic Trauma Life Support Instructor
   1986 Pediatric Advanced Life Support Provider and Instructor
   1987 Certified Base Station Physician for Los Angeles and Santa Clara Counties
   1992 Board Certified - American College of Emergency Medicine
   1993 Fellow - American College of Emergency Physicians
   1994 Board Certified Forensic Medical Examiner
   1995 Neonatal Advanced Life Support Provider
   1997 Fellow - American College of Forensic Medical Examiners

1997 Affiliate Faculty - Northern California Basic Trauma Life Support
1987 California Medical License No. G59661, DEA BL0859249
1990 Nevada Medical License No. 6566

3. I have also held and/or hold the following academic positions:

2006-present	Instructor at Harvard Medical School Beth Israel-Deaconesse Medical Center Department of Surgery
1990-present	Clinical Instructor at Stanford University
1990-1995	Assistant Clinical Professor at University of California San Francisco Department of Medicine
1989-1990	Acting Assistant Professor at Stanford University School of Medicine Department of Surgery/Emergency Medicine

4. Since 1993, I have been involved in creating new medical devices to treat patients with common illnesses, and I have started more than 10 companies directed to over 15 new technologies. In 1997, I founded Broncus Technologies, Inc., and Asthmatx, Inc. became a separate company from Broncus Technologies, Inc. in December of 2003. I am currently a Board Member and a paid consultant for Asthmatx, Inc., and hold option and stock interest in Asthmatx, Inc.

5. With respect to the subject matter of U.S. Patent Application No. 10/810,276, a person of ordinary skill in the art has a Medical Doctorate degree and 6 or more years of experience in treating patients with chronic and/or acute asthma.

6. I have carefully reviewed James et al., *The Mechanics of Airway Narrowing in Asthma*, Amr. Rev. Respir. Dis. Volume 139:242-246 (1989) ("James"); U.S. Patent No. 5,574,059 ("Regunathan"); U.S. Patent No. 5,053,033 ("Clarke"); and International Publication No. WO 97/37715 ("Waksman").

7. James describes mechanics of airway narrowing in asthma patients. James teaches that the airway walls of asthma patients are thickened by

chronic inflammation and concludes that such thickening of the airway walls could be as important as smooth muscle shortening in determining the airway responsiveness of these patients. (James at Summary.) James indicates that the airways of the asthmatic patients showed infiltration with inflammatory cells, thickening of the basement membrane, mucous gland and goblet cell prominence, and partial occlusion of the lumen with mucus and cellular debris. (James at p. 243, col. 3.) In addition, James discloses marked folding of the epithelium in some airways with a prominent circular layer of muscle. (James at p. 243, col. 3 to 244, col. 1.) The increase in wall thickness, therefore, is not confined to the airway smooth muscle, but rather it also includes the submucosa and epithelium. (James at p. 245, col. 1.) James, for example, teaches that the chronic inflammatory process present in the airway wall in patients with asthma is associated with (a) cellular infiltration, (b) deposition of connective tissue, (c) goblet cell metaplasia of the epithelium, and (d) an inflammatory exudate containing mucus in the airway lumen in addition to hypertrophy of smooth muscle. (James at p. 246, col. 1.) James further teaches that an important feature of asthma treatments at that time was the rapid reversibility of airway obstruction with drugs that relax smooth muscle. (James at p. 245, col. 3.) According to James, bronchodilation does not need to be limited to reversal of excessive smooth muscle contraction, but rather reversing the muscle contraction can also be applied for non-excessive muscle contraction of thickened airway walls to increase airway caliber and lower the resistance to a similar degree. (James at p. 245, col. 3.) Based on these findings, James concludes that changes produced by chronic inflammatory processes can lead to excessive airway narrowing without excessive smooth muscle contraction such that the treatment of asthma should focus on (a) reversing the inflammatory changes in the airway wall and (b) relaxation of the airway smooth muscle. (James at p. 246, col. 1.) James, however, does not disclose anything with respect to causing a change in mucus gland cells.

8. Before the present invention, there were several teachings in the prior art that airway smooth muscle was of the utmost importance and was indispensable for respiration. (Macklin, C.C., *The Musculature of the Bronchi and Lungs*, Physiol. Rev. (1929) 9:1-60.) As set forth in Mitzner, W., *Airway Smooth Muscle The Appendix of the Lung*, American Journal of Critical Care Medicine, (2004) 169:787-790 ("Mitzner"), the early body of literature dating back over a 125 year period taught that airway smooth muscle had one or more functional purposes. Although Mitzner cites later articles as refuting some of the functional purposes of airway smooth muscle, Mitzner also points out that other listed functional purposes were still thought to be valid as late as 2004 (e.g., peristalsis to assist exhalation). Therefore, in 1998, a person of ordinary skill in the art would have understood that airway smooth muscle had a functional purpose and that airway smooth muscle cells should not be killed.

9. In 1998, the United States Food and Drug Administration also held the prevailing view of the time that airway smooth muscle was important for normal lung function. This was one reason why the United States Food and Drug Administration did not grant Asthmatx, Inc. approval to treat asthma in a human patient by debulking airway smooth muscle tissue until 2005. For example, in response to an Investigational Device Exemption application regarding Asthmatx's Alair System, the USFDA stated:

> Airway smooth muscle facilitates airway dilation as well as airway constriction. Of concern is that ablation of airway smooth muscle in small bronchi may have negative effects by preventing airway dilation during sympathetic stimulation, e.g., during exercise. Patients could conceivably continue to have asthma attacks with secretions and smaller airway bronchospasm and then be unable to effectively cough and clear these secretions due to lack of larger airway smooth muscle tone. Reduced smooth muscle support of the conducting airways, coupled with underlying asthma, could lead to complications such as bronchiectasis.

(USFDA Letter dated 16 February 2001 regarding IDE No. G010016 attached in redacted format.)

10. James does not teach or otherwise suggest debulking or reducing the mass of the airway smooth muscle to reverse inflammatory changes for treating asthma. First, James teaches that the increase in airway wall thickness associated with asthma is not confined to the airway smooth muscle, but rather inflammation of the submucosa and the epithelium also contribute to the increased airway wall thickness. Second, James does not teach any mechanism to reverse the inflammation of the airway wall. Third, as explained in Paragraph 8 above, a person of ordinary skill in the art in 1998 would have understood that destruction or removal of airway smooth muscle was controversial because the prevailing view at that time was that airway smooth muscle performed a functional purpose essential to normal lung function. Therefore, in 1998, a person skilled in the art would not understand James to mean that asthma should, or even could, be treated by debulking the airway smooth muscle.

11. James expressly teaches that the treatment of asthma should focus on reversing the inflammatory changes in the airway wall and relaxation of the airway smooth muscle. A person of ordinary skill in the art would understand that reversing inflammatory changes in the airway involves acute reversal of inflammation of the submucosa and epithelium as opposed to debulking the airway smooth muscle because (a) the prevailing view in 1998 was that airway smooth muscle had a functional purpose and therefore should not be killed, (b) debulking does not provide acute relief, and (c) pharmaceutical treatment of the epithelium may provide acute relief.

12. Regunathan discloses that vascular hyperplasia, i.e., the excessive proliferation and hypertrophy of vascular smooth muscle cells, is a major pathogenic mechanism contributing to vascular pathology in atherosclerosis, hypertension resulting from renal artery stenosis and other causes, restenosis of coronary and other arteries after coronary angioplasty, insertion of vascular stents, and other conditions.

(Regunathan at 1:17-27.) The invention of Regunathan is directed to a non-invasive method of inhibiting the initiation or progression of vascular hyperplasia and, in particular, to inhibiting proliferation of vascular smooth muscle cells. (Regunathan at 1:34-37.) Regunathan, more specifically, teaches a method of inhibiting the proliferation of vascular smooth muscle cells by administering a vascular smooth muscle cell anti-proliferative effective amount of an I_2 imidazoline receptor agonist. (Regunathan at 1:37-42.) Regunathan, however, does not disclose anything with respect to causing a change in mucus gland cells.

13. Clarke is directed toward inhibiting restenosis associated with angioplasty and teaches that intimal hyperplasia or proliferation of vascular smooth muscle cells is a major factor in restenosis. (Clarke at 1:1-5 and 1:41-43.) Clarke further teaches vascular smooth muscle cells enter their growth cycle 2-3 days after injury and the majority of the vascular smooth muscle cells cease to proliferate within 7 days after injury. (Clarke at 1:43-50.) Clarke indicates that the total number of smooth muscle cells reaches a peak about two weeks after injury and remains constant for up to one year; Clarke states this suggests that a reduction of the number of smooth muscle cells injured during angioplasty will reduce the likelihood of subsequent restenosis. (Clarke at 1:50-55.) To inhibit restenosis, Clarke teaches reducing the proliferation of additional vascular smooth muscle cells in the blood vessel walls at an angioplasty site by irradiating the angioplasty site with the appropriate radiation in the UV wavelength range. (Clarke at 2:39-44.) The irradiation kills a major portion of the injured smooth muscle cells in the media so that few, if any, smooth muscle cells remain in the angioplasty site to proliferate and cause restenosis. (Clarke at 5:1-9.) However, as shown in Figures 3B and 3C, the thickness of media is not reduced by the process. Clarke does not disclose anything with respect to causing a change in mucus gland cells.

14. Waksman discloses an apparatus for delivering radioactive treatment from a radionuclide to tissue that has been damaged. Waksman teaches that the healing process in response to an injury is an overgrowth of tissue caused by increased cell proliferation that renarrows the lumen. (Waksman at 1:17-20.) In particular, Waksman teaches applying radiation from a radionuclide to prevent or inhibit hyperplasia following a balloon angioplasty procedure. (Waksman at 5:13-18 and 6:19-25.) Waksman provides a long list of vascular applications and also a list of non-vascular applications, including the bronchi and lungs, in which his invention may be useful. (Waksman 5:18 - 6:5.) However, in all of the applications, Waksman's invention is directed toward treating an area that has been damaged by an earlier procedure by inhibiting the proliferation of additional cells. Waksman, moreover, does not disclose anything with respect to causing a change in mucus gland cells.

15. In 1998, as well as now, a person of ordinary skill in the art would have understood that the purpose of both Regunathan, Clarke and Waksman was to inhibit injured vascular smooth muscle cells from producing additional vascular smooth muscle cells that would normally occur in response to damage, injury or other trauma to the vessel wall. With respect to vascular structures, restenosis is caused by hyperplasia as opposed to hypertrophy of smooth muscle cells. Hyperplasia in vascular applications is the excessive proliferation of new or additional cells above the level of normal cell production, whereas hypertrophy is the increase in tissue size caused by the filling with connective and scar tissue without necessarily increasing the number of smooth muscle cells above normal levels. A person of ordinary skill in the art would accordingly understand that Regunathan, Clarke and Waksman are limited to methods for reducing or inhibiting injured vascular smooth cells from producing additional smooth muscle cells to prevent hyperplasia.

16. Additionally, to a person of ordinary skill in the art, neither Regunathan nor Clarke nor Waksman teaches debulking or otherwise removing uninjured vascular smooth muscle tissue that existed before the injury occurred. First, Regunathan, Clarke and Waksman are all clear that hyperplasia (i.e., an increase in the number of cells) as opposed to hypertrophy (i.e., an increase in tissue size caused by the filling with connective and scar tissue) causes restenosis. Second, Regunathan, Clarke and Waksman teach methods for inhibiting the production of additional smooth muscle cells, but neither reference discloses debulking uninjured smooth muscle tissue that existed before injuring the vessel. Third, vascular smooth muscle provides an essential function for maintaining blood pressure through vasoconstriction and vasodilation, and as such a person skilled in the art would not apply the methods taught in Regunathan, Clarke and/or Waksman in a manner that would debulk the existing vascular smooth muscle tissue. Therefore, without an injury or other condition that causes proliferation of the smooth muscle tissue, a person of ordinary skill in the art would not apply the methods taught by Clarke, Regunathan and/or Waksman to airway smooth muscle or any other smooth muscle tissue in the body.

17. On 10 June 1998, I filed the present application directed to radical methods for treating asthma. In one embodiment the method includes selecting an airway that has hypertrophied airway smooth muscle, and irradiating a length of the airway with a light source. The light source has a wavelength of about 240 nm to about 280 nm and an intensity that causes a change in the airway such that a thickness of the airway smooth muscle decreases and bronchoconstriction of the airway is reduced. Another embodiment of the method includes selecting an airway for treatment and irradiating a length of the airway with a light source. The light source of this embodiment has a wavelength of about 240 nm to about 280 nm and an intensity which causes a change in the airway mucus gland cells such that mucus secretions of the airway are reduced.

18. In an asthmatic lung, the increase in thickness of the airway smooth muscle is caused by hypertrophy - not hyperplasia. As such, the airway smooth muscle does not suffer from an abnormally high proliferation of additional cells, but rather it is the increase in size of the uninjured airway tissue that contributes to the increase in airway wall thickness. By debulking the airway smooth muscle as set forth in several embodiments of my invention, the mass of the airway smooth muscle is reduced so as to reduce the ability of the airway to contract. This directly contradicts the position that Clarke's method would be applied to an asthmatic lung in accordance with the claimed method to decrease hypertrophy.

19. A person of ordinary skill in the art would not irradiate an uninjured airway wall of an asthmatic lung at a wavelength and intensity that, over time, would debulk airway smooth muscle based on the teachings of James, Regunathan, Clarke or Waksman, either individually or collectively. Clarke teaches applying the UV radiation in a manner that kills a portion of the injured smooth muscle cells to prevent or inhibit additional smooth muscle cells from proliferating. Clarke, in effect, proactively kills injured smooth muscle cells before their growth cycle to prevent the proliferation of additional cells. However, as explained above in Paragraph 16, without an injury or other condition that causes proliferation of smooth muscle cells, there is no reason to apply Clarke's method to airway smooth muscle or any other smooth muscle. Clarke accordingly does not teach debulking the smooth muscle cells, and a person of ordinary skill in the art would not apply Clarke in a manner that would cause such debulking because, at least in part, vascular smooth muscle provides an essential function for maintaining blood pressure. Regunathan and Waksman similarly teaches inhibiting proliferation of smooth muscle cells as opposed to debulking the smooth muscle tissue. Lastly, James does not teach debulking the airway smooth muscle, and a person of ordinary skill in the art in 1998 would not understand James to mean that asthma should, or even could, be treated by debulking the airway smooth muscle. Unlike the

cited references that are directed to preventing the proliferation of smooth muscle cells, several embodiments of my treatment seek to debulk existing uninjured airway smooth muscle affected by hypertrophy to provide a cure for chronic conditions. Therefore, it would not have been obvious to a person of ordinary skill in the art at the time of the invention to use the method of Clarke to treat asthma in light of the teachings of Regunathan, Waksman and James.

20. Additionally, even if Clarke's method was applied to an asthmatic airway, it would not result in debulking of the airway smooth muscle tissue. Vascular structures and airway structures are significantly different such that Clarke's method would be ineffective for debulking airway smooth muscle. Unlike the smooth lining of the endothelium in blood vessels, the epithelium in asthmatic airways has several folds (see, e.g., Figure 1 of filed application). Clarke teaches applying the UV radiation at a relatively low angle to the lumen wall that would result in shadowing within the airway such that some of the airway smooth muscle would not be treated, or at least not sufficiently treated, for debulking. The airway epithelium, which is comprised of tight junctions of columnar cells, is 10-15 times thicker than the single flat layer of squamous cells that comprise the vascular endothelium. Further, the airway epithelium necessarily facilitates diffusion of nitrogen for proper lung function while the endothelium prevents nitrogen diffusion and nitrogen-containing substances, and nitrogen monoxide in particular, which has a direct affect on causing vascular smooth muscle to contract, which could be catastrophic in an airway. The airway epithelium and blood vessel endothelium are accordingly two different materials with different properties that react differently to irradiation. As a result, a person of ordinary skill in the art would understand that the intensity level of Clarke's UV radiation to treat restenosis in a blood vessel would not likely be sufficient to debulk airway smooth muscle through the epithelium of an airway.

21. Also, a person of ordinary skill in the art would not be motivated or otherwise think of applying radiation to effect a change in the airway mucus gland cells such that mucus secretions of the airway are reduced based on James, Regunathan, Clarke, Waksman and/or the knowledge of a person of ordinary skill in the art at the time of the invention. Regunathan, Clarke and Waksman are all directed to treating portions of the vasculature that have been damaged by earlier medical procedures to inhibit or prevent the proliferation of additional smooth muscle cells. Nothing in these references teaches that mucus gland cells should or even could be changed. The vasculature, moreover, does not even have mucus gland cells such that there is no reason to believe that the methods taught by Regunathan, Clarke and/or Waksman have any application to airway mucus gland cells. Therefore, a person of ordinary skill in the art would not be motivated or otherwise think of applying radiation according to Clarke or Waksman to effect a change in the airway mucus gland cells such that mucus secretions of the airway are reduced.

22. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

7/21/2008
Date

Michael D. Lauer, M.D.

Attachment 1a

USFDA Letter dated 16 February 2001, regarding IDE No. G010016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 16 2001

Mr. Timothy R. Williams
Director of Regulatory and Clinical Affairs
Broncus Technologies, Inc.
1400 N. Shoreline Boulevard Bldg. A, Suite 8
Mountain View, CA 94043

Re: IDE Number G010016
Alair System
Dated: January 17, 2001
Received: January 18, 2001

Dear Mr. Williams:

The Food and Drug Administration (FDA) has reviewed your investigational device exemptions (IDE) application. We regret to inform you that your application is disapproved and you may not begin your investigation. Please be advised that, based on the data that you have provided, we believe that studies in humans pose significant potential risks that appear to outweigh the potential benefits. Our disapproval is based on the following deficiencies:

1. You provided pre-clinical data using the canine model. In total, there were nine animal studies performed to support this IDE application, with a total of 37 canines treated and over 2300 device activations.

   You have also provided the results of data collected outside of the United States (OUS) trial where one lobe was treated in 8 patients, 1 to 3 weeks before a scheduled lobectomy. There were 3 to 9 activations in each patient, for a total of 41 activations.

Even if normal healing of the larger treated bronchi were to occur, there are significant concerns that the underlying condition (asthma) would nonetheless remain. Airway smooth muscle facilitates airway dilation as well as airway constriction. Of concern is that ablation of airway smooth muscle in small bronchi may have negative effects by preventing airway dilation during sympathetic stimulation, e.g., during exercise. Patients could conceivably continue to have asthma attacks with secretions and smaller airway bronchospasm and then be unable to effectively cough and clear these secretions due to lack of larger airway smooth muscle tone. Reduced smooth muscle support of the conducting airways, coupled with underlying asthma, could lead to complications such as bronchiectasis.

If you submit information correcting the deficiencies, we will reevaluate your application. The information should be identified as an IDE amendment referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

Alternatively, you may request a regulatory hearing regarding the disapproval of your IDE application. The enclosure "Procedures to Request a Regulatory Hearing" describes how to submit such a request. The procedures governing a regulatory hearing are described in the regulations at 21 CFR Part 16.

If you prefer not to request a regulatory hearing, you may nevertheless request that this decision be reviewed by the IDE Review Committee within the Office of Device Evaluation (ODE). The enclosure entitled, "IDE Review Committee and Procedures to Request Review" discusses the purpose and operation of the Committee as well as how to submit such a request to the Committee.

If you have any questions, please contact Frank Lacy at (301) 443-8517 ext-170.

Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular and
Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures
(1) Procedures to Request a Regulatory Hearing
(2) IDE Review Committee and Procedures to Request Review

APPENDIX C

In the related proceedings referenced in Section II above, no answers from the Examiner or decisions from the Board of Patent Appeals and Interference have been filed. As such, copies of decisions in related proceedings are not provided.